RESEARCH ON MICROBIAL BIOFILMS

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National Institute of Dental and Craniofacial Research (NIDCR)
(http://www.nidcr.nih.gov)
National Institute of Allergy and Infectious Diseases (NIAID)
(http://www.niaid.nih.gov/)
National Institute on Deafness and Other Communication Disorders (NIDCD)
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National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS)
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National Institute of General Medical Sciences (NIGMS)
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National Heart, Lung, and Blood Institute (NHLBI)
(http://www.nhlbi.nih.gov)
National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK)
(http://www.niddk.nih.gov/)
National Institute of Biomedical Imaging and Bioengineering (NIBIB)
(http://www.nibib.nih.gov)

THIS PA CONTAINS THE FOLLOWING INFORMATION

o Required Federal Citations

PURPOSE OF THIS PA

The NIH Institutes listed above invite research grant applications to conduct studies on microbial biofilms leading to improved strategies to diagnose, prevent and treat biofilm-associated infectious diseases. Collaborative projects, both domestic and international, that bring together investigators in diverse scientific disciplines studying biofilms, including microbiology, immunology (including mucosal immunology), biochemistry, clinical medicine, pathology, bioengineering, material science, imaging technology, and mathematical modeling are encouraged.

RESEARCH OBJECTIVES

Background

A biofilm is an accumulation of microorganisms (bacteria, fungi, and/or protozoa, with associated bacteriophages and other viruses) embedded in a polysaccharide matrix and adherent to solid biologic or non-biologic surface. Biofilms are medically important, accounting for over 80 percent of microbial infections in the body. Examples include infections of the: oral soft tissues, teeth and dental implants; middle ear; gastrointestinal tract; urogenital tract; airway/lung tissue; eye; urinary tract prostheses; peritoneal membrane and peritoneal dialysis catheters, indwelling catheters for hemodialysis and for chronic administration of chemotherapeutic agents (Hickman catheters); cardiac implants such as pacemakers, prosthetic heart valves, ventricular assist devices, and synthetic vascular grafts and stents; prostheses, internal fixation devices, percutaneous sutures; and tracheal and ventilator tubing. The microorganisms tend to be far more resistant to antimicrobial agents and to be particularly difficult for the host immune system to render an appropriate response.

The need for increased research on biofilms is based on many factors:

- Biofilms are remarkably difficult to treat with antimicrobials. The reasons for this are not clear. Antimicrobials may be readily inactivated or fail to penetrate into the biofilm. In addition, bacteria within biofilms have increased (up to 1000-fold higher) resistance to antimicrobial compounds, even though these same bacteria are sensitive to these agents if grown under planktonic conditions.

- Biofilms increase the opportunity for gene transfer between/among bacteria.

This is important since bacteria resistant to antimicrobials or chemical biocides can transfer the genes for resistance to neighboring susceptible bacteria. Gene transfer can convert a previous avirulent commensal organism into a highly virulent pathogen.

- Certain species of bacteria communicate with each other within the biofilm.
As their density increases, the organisms secrete low molecular weight molecules that signal when the population has reached a critical threshold. This process, called quorum sensing, is responsible for the expression of virulence factors. For example, Pseudomonas aeruginosa produces destructive proteinases when the number of these bacteria reach a high enough density in the airway biofilms of cystic fibrosis patients.

- Bacteria express new, and sometimes more virulent phenotypes when growing within a biofilm. Such phenotypes may not have been detected in the past because the organisms were grown on rich nutrient media under planktonic conditions. The growth conditions are quite different particularly in the depths of biofilms, where nutrients and oxygen are usually limited, and waste products from neighbors can be toxic. In short, bacteria found at the bottom of the biofilm look and act different than species located at the surface.

- Bacteria embedded within biofilms are resistant to both immunological and non- specific defense mechanisms of the body. Contact with a solid surface triggers the expression of a panel of bacterial enzymes, which catalyze the formation of sticky polysaccharides that promote colonization and protection. The structure of biofilms is such that immune responses may be directed only at those antigens found on the outer surface of the biofilm, and antibodies and other serum or salivary proteins often fail to penetrate into the biofilm. In addition, phagocytes are unable to effectively engulf a bacterium growing within a complex polysaccharide matrix attached to a solid surface. This causes the phagocyte to release large amounts of pro-inflammatory enzymes and cytokines, leading to inflammation and destruction of nearby tissues.

The field of biofilm research has traditionally been hindered by an inability to study the biofilm in non-destructive, three dimensional ways. In addition, it has been difficult or impossible to assess gene expression and metabolism of the microbe at the single cell level within a biofilm. However, as a result of advances in laser technology, digital imaging, scanning electron microscopy, and new fluorescent probes, researchers can now build a three dimensional model of biofilms and identify the location in the biofilm where specific genes are being expressed.

This broad-based initiative on microbial biofilms is designed to elucidate the mechanisms underlying their formation as well as development of strategies for the prevention and treatment

of microbial biofilm-associated diseases. Moreover, this initiative is intended to capitalize on contemporary research in immunology, microbiology, bio-engineering and computer technology that might synergize with current biofilm research.

Research Objectives and Scope

Since microbial biofilms are a major problem affecting diverse anatomical locations of the body, several components of the NIH have joined in this Program Announcement. Examples of relevant research topics are listed below; however the list should not be construed as complete or restrictive. Applicants are encouraged to propose other topics that address the overall goal of this initiative, which is to advance the understanding of the formation of biofilms, the means to control them, and their role in disease.

o Development of improved imaging of biofilms in situ;

o Development of improved clinically relevant in vitro and in vivo models of biofilms under specific in vivo conditions such as flow rate, nutrient content, and temperature;

o Development of better probes (genetic, metabolic, and immunological) for real-time analysis;

o Development of high throughput methods to identify genes and proteins that are differentially expressed in biofilms;

o Studies of quorum sensing/signaling molecules;

o Studies of the exchange of genetic material within biofilms;

o Studies of organic contaminants on substrata, and their influence on biofilm structure;

o Development of novel approaches to control pathogenic bacteria by, for example, devising strategies to favor growth of non-pathogenic microorganisms in biofilm communities;

o Studies of interactions of biofilms with host tissues and artificial implants;

o Development or use of novel agents, materials, or coatings for preventing or treating infections related to cardiovascular and pulmonary devices, and orthopaedic devices (artificial joints), internal fixation devices, percutaneous sutures, and engineered tissues;

o Studies of pathogenic mechanisms of microbes growing in biofilms;

o Elucidation of mechanisms of resistance of biofilms to antimicrobial agents;

o Studies of host immune responses, both innate and adaptive to biofilms;

o Studies of the potential role of biofilms and host response in the development of systemic inflammatory response syndrome, septic shock, acute respiratory distress syndrome, and multiple organ dysfunction syndrome in injured or critically ill patients, or in model systems reflecting these clinical conditions;

o Studies of infectious lung disease in cystic fibrosis;

o Studies on the potential of diagnostic procedures such as bronchoalveolar lavage and bronchoscopy to disturb local biofilm flora and inoculate distant locations;

o Development of mathematical models and computer simulations of biofilms;

o Development of the methodology for the prevention and control of biofilms from catheters, orthopaedic devices and other clinically important solid surfaces; and,

o Sex, gender or age related issues involved in biofilm formation, prevention or treatment.

MECHANISM(S) OF SUPPORT

This PA will use the NIH R01 and R21 award mechanisms. As an applicant, you will be solely responsible for planning, directing, and executing the proposed project.

The R21 proposals should have the potential for truly groundbreaking impact. Use of this mechanism to explore new biomedical approaches to address basic and applied research questions is encouraged. Applicants are encouraged to contact program staff for advice about choosing the appropriate grant mechanism. R21 applications may request up to a total of two years of support, and total direct costs for the two years cannot exceed $275,000.

The objective of the R21 mechanism is to support innovative, high risk/high impact research requiring preliminary testing or development; exploration of the use of approaches and concepts

new to biofilm research; research and development of new technologies, techniques or methods; or initial research and development of data upon which significant future research may be built. Applications will be considered as high impact if they demonstrate the potential for ground-breaking, precedent-setting significance, and high risk because they either lack sufficient preliminary data to ensure their feasibility, or involve using a new model system or technique. While this PA is intended to encourage innovation and high impact research, and while minimal preliminary data are expected to be described in the application, applications should clearly indicate that the proposed research and/or development is scientifically sound, that the qualifications of the investigators are appropriate, and that resources available to the investigators are adequate.

This PA uses just-in-time concepts. It also uses the modular as well as the non-modular budgeting formats(see http://grants.nih.gov/grants/funding/modular/modular.htm). Specifically, if you are submitting an application with direct costs in each year of $250,000 or less, use the modular format. Otherwise follow the instructions for non-modular research grant applications.

ELIGIBLE INSTITUTIONS

You may submit (an) application(s) if your institution has any of the following characteristics:

o For-profit or non-profit organizations
o Public or private institutions, such as universities, colleges, hospitals, and laboratories
o Units of State and local governments
o Eligible agencies of the Federal government
o Domestic or foreign
o Faith-based or community-based organizations

INDIVIDUALS ELIGIBLE TO BECOME PRINCIPAL INVESTIGATORS

Any individual with the skills, knowledge, and resources necessary to carry out the proposed research is invited to work with their institution to develop an application for support. Individuals from underrepresented racial and ethnic groups as well as individuals with disabilities are always encouraged to apply for NIH programs.

WHERE TO SEND INQUIRIES

We encourage your inquiries concerning this PA and welcome the opportunity to answer questions from potential applicants. Inquiries may fall into two areas: scientific/research and financial or grants management issues:

o Direct your questions about scientific/research issues to:

Dennis F. Mangan, Ph.D.
Division Basic and Translational Sciences
National Institute of Dental and Craniofacial Research
Building 45, Suite 18
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FAX: (301) 402-8318
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Peter Moy, Ph.D.
National Institute of Biomedical Imaging and Bioengineering
Democracy Two, Suite 200 MSC 5469
6707 Democracy Boulevard
Bethesda, MD 20892-5469
Telephone: (301) 496-9270
FAX: (301) 480-0679
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Division of Heart and Vascular Diseases
National Heart, Lung, and Blood Institute
6701 Rockledge Drive, Room 9146

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Division of Microbiology & Infectious Diseases
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FAX: (301) 496-8030
Email: ct18m@nih.gov

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Musculoskeletal Diseases Branch
National Institute of Arthritis and Musculoskeletal and Skin Diseases, NIH
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6701 Democracy Boulevard, Suite 800
MSC 4872
Bethesda, MD 20892-4872
Telephone: (301) 594-5055
FAX: (301) 480-4543
Email: jp149d@nih.gov

Scott Somers, Ph.D.
National Institute of General Medical Sciences

Building 45; Room 2AS-49
Bethesda, MD 20892
Telephone: (301) 594-5560
FAX: (301) 480-2802
Email: somerss@nigms.nih.gov

o Direct your questions about financial or grants management matters to:

Mary Daley
Chief Grants Management Officer
National Institute of Dental and Craniofacial Research
45 Center Drive MSC 6402
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Since Institute staff assignments may change during the course of this announcement, applicants should check the following website for the most recent contact information: http://www.nidcr.nih.gov/funding/contacts_PA_Biofilms2003.asp.

SUBMITTING AN APPLICATION

Applications must be prepared using the PHS 398 research grant application instructions and forms (rev. 5/2001). The PHS 398 is available at http://grants.nih.gov/grants/funding/phs398/phs398.html in an interactive format. For further assistance contact GrantsInfo, Telephone (301) 435-0714, Email: GrantsInfo@nih.gov.

APPLICATION RECEIPT DATES: Applications submitted in response to this program announcement will be accepted at the standard application deadlines, which are available at http://grants.nih.gov/grants/dates.htm. Application deadlines are also indicated in the PHS 398 application kit.

SPECIFIC INSTRUCTIONS FOR MODULAR GRANT APPLICATIONS: Applications requesting up to $250,000 per year in direct costs must be submitted in a modular grant format. The modular grant format simplifies the preparation of the budget in these applications by limiting the level of budgetary detail. Applicants request direct costs in $25,000 modules. Section C of the research grant application instructions for the PHS 398 (rev. 5/2001) at

http://grants.nih.gov/grants/funding/phs398/phs398.html includes step-by-step guidance for preparing modular grants. Additional information on modular grants is available at http://grants.nih.gov/grants/funding/modular/modular.htm.

SUPPLEMENTAL INSTRUCTIONS:

R21 Applications: All application instructions outlined in the PHS 398 application kit are to be followed with the following modifications for R21 applications:

1. FACE PAGE, Item 6: Up to a total of two years of support may be requested. Total direct costs for the two years cannot exceed $275,000.

2. Items a-d of the Research Plan for the R21 application may not exceed fifteen (15) pages, including tables and figures. The following information should be taken into account for items a, b and c:

o Item a, SPECIFIC AIMS--The instructions for this section suggest that the applicant state "the hypotheses to be tested". Since some applications submitted in response to this PA may also be design- or problem-driven (e.g., development of novel technologies), or need-driven (initial research to develop a body of data upon which future research will build), hypothesis testing per se may not be the driving force in developing such a proposal and, therefore, may not be applicable. The application should state the hypotheses, design, problem and/or need which will drive the proposed research.

o Item b, BACKGROUND AND SIGNIFICANCE--In this section, it is important to identify clearly how the application addresses the specific objectives of this PA and the purpose of the R21 mechanism.

o Item c, PRELIMINARY STUDIES/PROGRESS REPORT—No preliminary data are required for an R21 application.

3. APPENDIX - Up to five articles can be submitted in the appendix.

SPECIFIC INSTRUCTIONS FOR APPLICATIONS REQUESTING $500,000 OR MORE PER YEAR:

Applications requesting $500,000 or more in direct costs for any year must include a cover letter identifying the NIH staff member within one of the NIH institutes or centers (IC) who has agreed to accept assignment of the application.

Applicants requesting $500,000 or more must carry out the following steps:

1) Contact the IC program staff at least 6 weeks before submitting the application, i.e., as you are developing plans for the study;

2) Obtain written agreement from the IC staff that the IC will accept your application for consideration for award; and,

3) Identify, in a cover letter sent with the application, the staff member and IC who agreed to accept assignment of the application.

This policy applies to all investigator-initiated new (type 1), competing continuation (type 2), competing supplement, or any amended or revised version of these grant application types. Additional information on this policy is available in the NIH Guide for Grants and Contracts, October 19, 2001 at http://grants.nih.gov/grants/guide/notice-files/NOT-OD-02-004.html.

SENDING AN APPLICATION TO THE NIH: Submit a signed, typewritten original of the application, including the checklist, and five signed photocopies in one package to:

Center for Scientific Review
National Institutes of Health
6701 Rockledge Drive, Room 1040, MSC 7710
Bethesda, MD 20892-7710
Bethesda, MD 20817 (for express/courier service)

APPLICATION PROCESSING: Applications must be received by or mailed on or before the receipt dates described at http://grants.nih.gov/grants/funding/submissionschedule.htm. The CSR will not accept any application in response to this PA that is essentially the same as one currently pending initial review unless the applicant withdraws the pending application. The CSR will not accept any application that is essentially the same as one already reviewed. This does not preclude the submission of a substantial revision of an application already reviewed, but such application must include an Introduction addressing the previous critique.

PEER REVIEW PROCESS

Applications submitted for this PA will be assigned on the basis of established PHS referral guidelines. An appropriate scientific review group convened in accordance with the standard NIH peer review procedures (http://www.csr.nih.gov/refrev.htm) will evaluate applications for scientific and technical merit.

As part of the initial merit review, all applications will:

o Receive a written critique
o Undergo a selection process in which only those applications deemed to have the highest scientific merit, generally the top half of applications under review, will be discussed and assigned a priority score
o Receive a second level review by the appropriate national advisory council or board.

REVIEW CRITERIA

The goals of NIH-supported research are to advance our understanding of biological systems, improve the control of disease, and enhance health. In the written comments, reviewers will be asked to discuss the following aspects of your application in order to judge the likelihood that the proposed research will have a substantial impact on the pursuit of these goals:

o Significance
o Approach
o Innovation
o Investigator
o Environment

The scientific review group will address and consider each of these criteria in assigning your application's overall score, weighting them as appropriate for each application. Your application does not need to be strong in all categories to be judged likely to have major scientific impact and thus deserve a high priority score. For example, you may propose to carry out important work that by its nature is not innovative but is essential to move a field forward.

(1) SIGNIFICANCE: Does your study address an important problem? If the aims of your application are achieved, how do they advance scientific knowledge? What will be the effect of these studies on the concepts or methods that drive this field?

(2) APPROACH: Are the conceptual framework, design, methods, and analyses adequately developed, well integrated, and appropriate to the aims of the project? Do you acknowledge potential problem areas and consider alternative tactics?

(3) INNOVATION: Does your project employ novel concepts, approaches or methods? Are the aims original and innovative? Does your project challenge existing paradigms or develop new methodologies or technologies?

(4) INVESTIGATOR: Are you appropriately trained and well suited to carry out this work? Is the work proposed appropriate to your experience level as the principal investigator and to that of other researchers (if any)?

(5) ENVIRONMENT: Does the scientific environment in which your work will be done contribute to the probability of success? Do the proposed experiments take advantage of unique features of the scientific environment or employ useful collaborative arrangements? Is there evidence of institutional support?

ADDITIONAL REVIEW CRITERIA: In addition to the above criteria, your application will also be reviewed with respect to the following:

PROTECTIONS: The adequacy of the proposed protection for humans, animals, or the environment, to the extent they may be adversely affected by the project proposed in the application.

INCLUSION: The adequacy of plans to include subjects from both genders, all racial and ethnic groups (and subgroups), and children as appropriate for the scientific goals of the research. Plans for the recruitment and retention of subjects will also be evaluated. (See Inclusion Criteria included in the section on Federal Citations, below)

BUDGET: The reasonableness of the proposed budget and the requested period of support in relation to the proposed research.

AWARD CRITERIA

Applications submitted in response to a PA will compete for available funds with all other recommended applications. The following will be considered in making funding decisions:

o Scientific merit of the proposed project as determined by peer review
o Availability of funds
o Relevance to program priorities

REQUIRED FEDERAL CITATIONS

MONITORING PLAN AND DATA SAFETY AND MONITORING BOARD: Research components involving Phase I and II clinical trials must include provisions for assessment of patient eligibility and status, rigorous data management, quality assurance, and auditing procedures. In addition, it is NIH policy that all clinical trials require data and safety monitoring, with the method and degree of monitoring being commensurate with the risks (NIH Policy for Data Safety and Monitoring, NIH Guide for Grants and Contracts, June 12, 1998: http://grants.nih.gov/grants/guide/notice-files/not98-084.html).

INCLUSION OF WOMEN AND MINORITIES IN CLINICAL RESEARCH: It is the policy of the NIH that women and members of minority groups and their sub-populations must be included in all NIH-supported clinical research projects unless a clear and compelling justification is provided indicating that inclusion is inappropriate with respect to the health of the subjects or the purpose of the research. This policy results from the NIH Revitalization Act of 1993 (Section 492B of Public Law 103-43).

All investigators proposing clinical research should read the AMENDMENT "NIH Guidelines for Inclusion of Women and Minorities as Subjects in Clinical Research - Amended, October, 2001," published in the NIH Guide for Grants and Contracts on October 9, 2001 (http://grants.nih.gov/grants/guide/notice-files/NOT-OD-02-001.html);
a complete copy of the updated Guidelines are available at http://grants.nih.gov/grants/funding/women_min/guidelines_amended_10_2001.htm.
The amended policy incorporates: the use of an NIH definition of clinical research; updated racial and ethnic categories in compliance with the new OMB standards; clarification of language governing NIH-defined Phase III clinical trials consistent with the new PHS Form 398; and updated roles and responsibilities of NIH staff and the extramural community. The policy continues to require for all NIH-defined Phase III clinical trials that: a) all applications or proposals and/or protocols must provide a description of plans to conduct analyses, as appropriate, to address differences by sex/gender and/or racial/ethnic groups, including subgroups if applicable; and b) investigators must report annual accrual and progress in conducting analyses, as appropriate, by sex/gender and/or racial/ethnic group differences.

INCLUSION OF CHILDREN AS PARTICIPANTS IN RESEARCH INVOLVING HUMAN SUBJECTS:

The NIH maintains a policy that children (i.e., individuals under the age of 21) must be included in all human subjects research, conducted or supported by the NIH, unless there are scientific and ethical reasons not to include them. This policy applies to all initial (Type 1) applications submitted for receipt dates after October 1, 1998.

All investigators proposing research involving human subjects should read the "NIH Policy and Guidelines" on the inclusion of children as participants in research involving human subjects that is available at http://grants.nih.gov/grants/funding/children/children.htm.

REQUIRED EDUCATION ON THE PROTECTION OF HUMAN SUBJECT PARTICIPANTS: NIH policy requires education on the protection of human subject participants for all investigators submitting NIH proposals for research involving human subjects. You will find this policy announcement in the NIH Guide for Grants and Contracts Announcement, dated June 5, 2000, at http://grants.nih.gov/grants/guide/notice-files/NOT-OD-00-039.html.

HUMAN EMBRYONIC STEM CELLS (hESC): Criteria for federal funding of research on hESCs can be found at http://grants.nih.gov/grants/stem_cells.htm and at http://grants.nih.gov/grants/guide/notice-files/NOT-OD-02-005.html. Only research using hESC lines that are registered in the NIH Human Embryonic Stem Cell Registry will be eligible for Federal funding (see http://escr.nih.gov). It is the responsibility of the applicant to provide the official NIH identifier(s)for the hESC line(s)to be used in the proposed research. Applications that do not provide this information will be returned without review.

PUBLIC ACCESS TO RESEARCH DATA THROUGH THE FREEDOM OF INFORMATION ACT: The Office of Management and Budget (OMB) Circular A-110 has been revised to provide public access to research data through the Freedom of Information Act (FOIA) under some circumstances. Data that are (1) first produced in a project that is supported in whole or in part with Federal funds and (2) cited publicly and officially by a Federal agency in support of an action that has the force and effect of law (i.e., a regulation) may be accessed through FOIA. It is important for applicants to understand the basic scope of this amendment. NIH has provided guidance at http://grants.nih.gov/grants/policy/a110/a110_guidance_dec1999.htm.

Applicants may wish to place data collected under this PA in a public archive, which can provide protections for the data and manage the distribution for an indefinite period of time. If so, the application should include a description of the archiving plan in the study design and include

information about this in the budget justification section of the application. In addition, applicants should think about how to structure informed consent statements and other human subjects procedures given the potential for wider use of data collected under this award.

URLs IN NIH GRANT APPLICATIONS OR APPENDICES: All applications and proposals for NIH funding must be self-contained within specified page limitations. Unless otherwise specified in an NIH solicitation, Internet addresses (URLs) should not be used to provide information necessary to the review because reviewers are under no obligation to view the Internet sites. Furthermore, we caution reviewers that their anonymity may be compromised when they directly access an Internet site.

HEALTHY PEOPLE 2010: The Public Health Service (PHS) is committed to achieving the health promotion and disease prevention objectives of "Healthy People 2010," a PHS-led national activity for setting priority areas. This PA is related to one or more of the priority areas. Potential applicants may obtain a copy of "Healthy People 2010" at http://www.health.gov/healthypeople.

AUTHORITY AND REGULATIONS: This program is described in the Catalog of Federal Domestic Assistance Numbers 93.121 (NIDCR), 93.856 (NIAID), 93.173 (NIDCD), 93.846 (NIAMS), 93.859 (NIGMS), 93.837 (NHLBI), 93.849 (NIDDK), 93.286 and 93.287 (NIBIB) and is not subject to the intergovernmental review requirements of Executive Order 12372 or Health Systems Agency review. Awards are made under authorization of Sections 301 and 405 of the Public Health Service Act as amended (42 USC 241 and 284) and administered under NIH grants policies described at http://grants.nih.gov/grants/policy/policy.htm and under Federal Regulations 42 CFR 52 and 45 CFR Parts 74 and 92.

The PHS strongly encourages all grant recipients to provide a smoke-free workplace and discourage the use of all tobacco products. In addition, Public Law 103-227, the Pro-Children Act of 1994, prohibits smoking in certain facilities (or in some cases, any portion of a facility) in which regular or routine education, library, day care, health care, or early childhood development services are provided to children. This is consistent with the PHS mission to protect and advance the physical and mental health of the American people.

Return to Volume Index
Return to NIH Guide Main Index

Department of Health
and Human Services

National Institutes of Health (NIH)
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